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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/707,548	11/06/00	SCHULTZ P	CHIR116472

027476
Chiron Corporation
Intellectual Property - R440
P.O. Box 8097
Emeryville CA 96662-8097

HM12/0509

EXAMINER	
BERCH,M	
ART UNIT	**PAPER NUMBER**
1624	5

DATE MAILED: 05/09/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/707,548	SCHULTZ ET AL.	
	Examiner	Art Unit	
	Mark L. Berch	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If the period for reply specified above is the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) 1-27 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-27 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15)☒ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18)☐ Interview Summary (PTO-413) Paper No(s). _____ .
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other:

DETAILED ACTION

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-27 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-26 of U.S. Patent No. 6153618. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the parent are just a little narrower than those here. With regard to claim 26 and 27, these would presumably be the intended consequences of the act of claim 25 of the patent.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 9 is rejected under 35 U.S.C. 112, paragraphs 1 and 2, as the claimed invention is not described, or is not described in such full, clear, and exact terms as to enable any person skilled in the art to make and use the same, and/or failing to particularly point out and distinctly claim the subject matter which applicant regards as his invention. Specifically:

R_1 is not a permitted choice because CF_3 is not a permitted substituent on the aralkyl. Hence, Claim 9 is not properly dependent (paragraph 2) and the specification has no teaching of how to use which embraces this species (paragraph 1).

Claims 1-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. The scope of "esters" is unclear. Are these esters when R_2 is OH or ester when R_1 has an OH substituent? In the former case, the provision for R_2 as appears superfluous, since this would already be covered by the ester language. Moreover, esters of what structure? If the esters are formed when R_1 has an OH substituent, what is the nature of the acid, since these esters are formed by replacing the H of the OH with an acyl from that acid. Does this embrace esters from acids of S? P? As? What does the stem look like, i.e. if the esters which forms the acid is e.g. YC(O)OH, what is Y?

2. The term "alkyl" has been rendered indefinite by the page 3 material, which covers cyclic terms such as cyclohexyl. That is not "alkyl" but "cycloalkyl"; the claims should be amended accordingly. Definitions selected cannot contradict the normal meaning of a term (*In re Hill*, 73 USPQ 482; *Ex Parte Clifford*, 63 USPQ 19). Removal of

"cyclic" from page 3, lines 18 and 20, and putting the cycloalkyl choices of line 22 into the cycloalkyl paragraph on page 4 will fix the matter.

Claim 26 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

There is no way of knowing at present what the scope of this claim actually is. Perhaps all diseases are covered. One of ordinary skill in the art could not determine the scope of this claim. This claim is essentially of the form "I claim it whenever somebody (else) can get it to work." The material at page 5 is completely generic. Further, it is so vaguely broad that it would cover circumstances where a person has too little GSK3 as their problem, which these compounds could obviously not deal with. It is broad enough to cover a circumstance where lowering the GSK3 levels brings no actual benefit to the patient.

Determining whether a given disease responds or does not respond to such inhibition will surely involve undue experimentation. Suppose that a given GSK3 Inhibitor X when administered to a patient with Disease D does not obtain a response. Does one then conclude that Disease D does not fall within this claim? Keep in mind that:

A. It may be that the next patient will respond. It is quite common for pharmaceuticals to work only with some people, not all. Thus, how many need to be tested?

B. It may be that the wrong dosage or dosage regimen was employed. It is quite common for pharmaceuticals to work at one dosage, but not at another which is significantly higher or lower. Furthermore, the dosage regimen may be vital --- should

the drug be given e.g. once a day, or four times in divided dosages? Thus, how many dosages and dosage regimens must be tried before one is certain that this pharmaceutical won't affect Disease D?

C. It may be that X simply isn't potent enough for Disease D, but that another inhibitor Y is potent enough, so that D really does fall within the claim. Thus, how many different inhibitors must be tried before one concludes that D doesn't fall within the claim?

D. Conversely, if D responds to Y but not to X, can one really conclude that D falls within the claim? It may be that the X result is giving the accurate answer, and that the success of Y arises from some other unknown property which Y is capable of. Thus, when mixed results are obtained, how many more pharmaceuticals need be tested?

E. Finally, suppose that X really will work, but only when combined with Z. There are for example, agents in the antiviral and anticancer technology which are not themselves effective, but the disease will respond when the agents are combined with something else.

F. In addition, literally speaking, any disorder can be treated with any drug, although the treatment might not be successful. Assuming that "successful treatment" is what is intended, what criterion is to be used? If one person in 10 responds to a given drug, does that mean that the disease is treatable? One in 100? 1,000? 10,000?

As a result, determining the true scope of the claim will involve extensive and potentially open-ended research. Without it, one skilled in the art cannot determine the actual scope of the claim. Hence, the claim is indefinite.

Claims 25-27 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment of NIDDM, does not reasonably

provide enablement for the broad scope as claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

GSK3 is one of several hundred protein kinases that have already been identified. It is one of a number of enzymes that are involved with the hyperphosphorylation of the tau protein. This hyperphosphorylation and/or the body's failure to provide for adequate dephosphorylation provides an important constituent in the neurofibrillary tangles seen in Alzheimer's Disease patients. However, this does not mean that one of ordinary skill in the art in this art would know how to make a GSK3 inhibitor effective for the treatment of Alzheimer's Disease. As evidence of this is cited Pelech (Neurobiology of Aging Vol. 16(3) 247, 1995). The last sentence of the abstract conveys this clearly: "A detailed understanding of proline-directed kinase dependent pathways may permit the identification of rational targets for the therapeutic intervention of Alzheimer's Disease and other neurological disorders." It is clear from this sentence that research in this area is still at a very early stage. What needs to come next is a "detailed knowledge of ... pathways". And from that will emerge "rational targets for the therapeutic intervention" This is clearly a description of basic research, not routine experimentation. The rational targets themselves have not been yet identified. The article makes clear the complexity of the situation and the limits of what is understood. There appear to be at least three different mechanisms of the activation of MAP kinases (see figures 2, 3 and 4). Involved in this hyperphosphorylation process are three different categories of kinases, including the proline directed kinases (of which GSK3 is an example), cyclin dependent kinases and MAP kinases. Each category has a variety of different kinases present, and even GSK3 exists is two isoforms. These two forms are

not the same; as the article notes, the form is inhibited by PKC, but not the form. The entire concept of being able to use this information for the actual treatment of Alzheimer's Disease isn't even mentioned.

Applicants in the parent pointed to the page 253 statement in Pelech, "These kinases represent rational targets for drug design." They do indeed, but the sentence means only what it says, not that such a utility is enabled. The sentence says, in effect, that this represents a reasonable research strategy to pursue. The research so far offers "fresh hope for the development of new and effective therapeutics" (from the previous sentence). But "fresh hope" falls substantially short of the notion that one of ordinary skill in the art could inhibit or treat Alzheimer's Disease without undue experimentation. The last sentence of the abstract makes it clear that what is still needed is a "detailed understanding of proline-directed kinase dependent pathways" Indeed, the paper doesn't even zero in on GSK3 or even firmly establish what the origin of tau protein hyperphosphorylation is. Instead, the paper says things like, "If aberrant activation of either MAP kinase, GSK3 or CDK5 is at the root of Alzheimer's Disease, then defective regulation at multiple points upstream of these kinases could produce similar results." Note that a) the "If" means that its just suggested as a possibility, b) GSK3 is just one of several candidates, and c) the sentence doesn't say that one of ordinary skill in the art would know what to do about this "defective regulation at multiple points upstream of these kinases". This is a vast distance from saying that one of ordinary skill in the art would known how to use GSK3 inhibitors to accomplish anything.

Much the same teaching is provided by Imahori (J. Biochem. 121, 179(1997). This work (which is a little later than the provisional application date here) establishes that

the known Tau Protein Kinase is actually a mixture of two active enzymes, TPKI and TPKII, the latter of which is the form of GSK3 . Much research is presented in support of an eventual conclusion that these two enzymes "could account for most, but not all, of the major phosphorylation sites of fetal tau and PHF-tau". These act in a concerted manner. Despite this tremendous amount of work, the notion of being able to use this information for the actual treatment of Alzheimer's Disease isn't even mentioned. That provides indirect evidence that this research isn't at the stage where only routine experimentation remains. It should also be noted that the form of GSK3 isn't even mentioned, and the inference seems to be that it is not involved.

Briscoe (Current Biology 5(3) 228 (1995)) and Welsh (Trends in Cell Biology 6(7) 274 (1996)) highlight the role of GSK3 in receptor regulation, cell signaling, neural patterning, etc. Again, no mention is made of how to use this information for therapeutic purposes.

Accordingly, this utility is not enabled. No evidence is seen that one of ordinary skill in the art would be able to use GSK3 for the treatment of Alzheimer's Disease. None of the references cited by applicants teach that GSK3 inhibitors generally would be expected to treat diabetes. Further, Claim 25 doesn't even require that any disorder actually be treated, or any biological effect takes place, as this covers just contacting GSK3 with the compound, which could be done in a beaker. There is no possible use of the bare process of contacting the compound with the enzyme, which is all that the claim actually specifies.

In the parent, applicants cited other references, but have not done so here. IF these are introduced to this case, the examiner will rely on statements made in the parent.

In the parent, applicants cited *Cross vs. Iizuka*, 224 USPQ 739. But the facts were very different there. Cross had a specific enzyme, the inhibition of which was considered in the art to be useful per se for the treatment of asthma. Further, this was bolstered by the fact that structurally related compounds showed the same utility in vitro and in vivo. Determining the correct dosage could be done "without inventive skill or undue experimentation", so that under these circumstances, an in vitro test "may establish a practical utility". Applicants appear to be reading the decision as saying that any sort of in vitro test automatically establishes enablement. The decision says nothing of the sort, and indeed cautions, "Every utility question ... must be decided on its own factual circumstances." In that case, the in vitro test did provide a reasonable correlation to actual activity. Here, by contrast, it is clear that the art was nowhere near as advanced as it was in *Cross vs. Iizuka*, so a different result is appropriate.

Indeed, the facts here are closer to those of Hoffman v. Klaus, 9 USPQ 2d 1657, 1660: "We find no evidence before us here that one skilled in the art at the time the tests were performed would have been reasonably certain that merely because CP-57,850 inhibited the production of collagenase in the in vitro test, it had practical utility. There is no evidence that there was a reasonable correlation between tests and the treatment of arthritis or for any other useful purpose." The two decisions taken together make it clear that these circumstances must be approached individually, on the factual basis of what is known at the time. Here, the examiner has presented evidence that the skill level in this art was not such that one could go from enzyme inhibition to practical utility; indeed, such a prospect is generally not even mentioned. In fact, just the opposite is presented as the case. Pelech especially sets forth that fundamental research

lies ahead before "rational targets for the therapeutic intervention of Alzheimer's Disease." can be identified.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark L. Berch whose telephone number is 703-308-4718. The examiner can normally be reached on M-F 7:15 - 3:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mukund Shah can be reached on 308-4716. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4556 for regular communications and 703-308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 708-308-1235.

Mark L. Berch
Primary Examiner
Art Unit 1624

May 7, 2001